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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/628,667	07/28/2000	David Putnam	10436-0010-999	3663

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EXAMINER
EPPERSON, JON D

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 11/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/628,667	PUTNAM ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *136-156 and 158-177* is/are pending in the application.

4a) Of the above claim(s) *137,138,142,143,148,156,159 and 164* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *136,139-141,144-147,149-155,158,160-163 and 165-177* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 July 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed July 7, 2005 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Status of the Claims

3. Claims 136-172 were pending. Applicants canceled claim 157 and amended claims 136, 152-155 and 168-172. In addition, claims 173-177 were added. Therefore, claims 136-156 and 158-177 are pending.

4. Claims 137, 138, 142, 143, 148, 156, 159 and 164 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim.

5. Therefore, claims 136, 139-141, 144-147, 149-155, 158, 160-163 and 165-177 are examined on the merits in this action.

Restriction

6. Please note: Applicant's elected species ((a) Paclitaxel, (b) polyethylene glycol, (c) UV, (d) increased solubility, (e) liquid sample, (g) tecan) was found in the art. Furthermore, Applicant's *specifically* elected species ((f) spotfire software) was searched and was not found in

the prior art. Thus, the search was expanded to non-elected species, which *were* found in the prior art, see rejections below. Also, see MPEP § 803.02 (emphasis added):

> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. ***The prior art search, however, will not be extended unnecessarily to cover all nonelected species.*** Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

7. Applicants' arguments with regard to the species election (e.g., see 7/7/05 Response, page 14) have been considered, but are not found persuasive. Applicants did not set forth a claim to their elected invention in the previous office action and, as a result, Applicants' arguments are moot. The Examiner is not required to set for "all" the art but, rather, only the "best" art (e.g., see MPEP § 706.02, "Prior art rejections should ordinarily be confined strictly to the best available art"). Furthermore, Applicant's amendment necessitated any new grounds of rejection presented in this Office action and thus finality is proper (see below).

Withdrawn Objections/Rejections

8. All rejections are withdrawn in view of Applicants' arguments and/or amendments.

New Rejections

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 136, 139-141, 144-147, 149-155, 158, 160-163 and 165-177 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sharma et al. (Sharma, U. S.; Balasubramanian, S. V.; Straubinger, R. M. "Pharmaceutical and Physical Properties of Paclitaxel (Taxol) Complexes with Cyclodextrins" *J. Pham. Sci.* **1995**, *84*, *10*, 1223-1230) and Merritt (Merritt, A. T. "Uptake of new technology in lead optimization for drug discovery" **1998** DDT, 3(11), 505-510) and Saneii et al. (U.S. Patent No. 5,746,982) (Date of Patent is **May 5, 1998**) and Wang et al. (Wang, T.; Zeng, L.; Strader, T.; Burton, L.; Kassel, D. B. "A New Ultra-high Throughput Method for Characterizing Combinatorial Libraries Incorporating a Multiple Probe Autosampler Coupled with Flow Injection mass Spectrometry Analysis" *Rapid Commun. mass Spectrom.* **1998** *12*, 1123-1129) and Lipinski et al. (Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings" Advanced Drug Delivery Reviews **1997**, *23*, 3-25).

For ***claims 136 and 155***, Sharma et al. (see entire document) teach a method for analyzing the increase in solubility of paclitaxel as a result of its interactions with a library of cyclodextrins, which reads on the claimed invention (e.g., see Sharma et al., abstract). For example, Sharma et al. disclose **(a)(1)** a library of samples that contain a component-in-common and one or more additional components (e.g., see Sharma et al., Table 1 wherein component-in-common = Paclitaxel and additional component = cyclodextrins). In addition, Sharma et al. disclose varying the identity of the one or more additional components or varying in the ratio of the volume of component-in-common to the volume of the one ore more additional components (e.g., see Sharma et al., Table 1 wherein the identity is varied, such as HEβ, HPβ, DMβ, etc.). Sharma et al. also disclose **(b)** testing each sample for a property to generate a data set (e.g., see Table 1, showing amount of Paclitaxel dissolved; see also figure 1; see also figure 2; see also Experimental section). Sharma et al. also disclose **(c)** analyzing the data set to measure or detect an interaction between components of the sample formulations, said interaction being increased solubility of the component-in-common (e.g., see Table 1, disclosing solubility "enhancement" factor that results from interaction of Paclitaxel with cyclodextrin). For claim 155, Sharma et al. also disclose the use of synergistic interactions between different cyclodextrins to achieve greater solubility with a lower renal and hemolytic toxicity (e.g., see page 1229, last paragraph).

For ***claims 139-141, 144, 149, 158, 160, 173 and 174***, Sharma et al. disclose Applicants' elected Paclitaxel therapeutic pharmaceutical in a liquid "dissolved" form (e.g., see Sharma et al., abstract).

For ***claims 145, 146, 161, 162***, Sharma et al. disclose the use of samples less than 100 ng of sample (e.g., see Sharma et al., Table 1; see also Lipinski et al. and Merritt references below). In addition, the Examiner notes "the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA1955). Also note that optimization of process steps, especially with respect to numbers of samples analyzed, numbers of substrate regions and quantity of sample used is within the routine skill of the art. *In re Burhans*, 154 F.2d 690, 69 USPQ330 (CCPA 1946) (selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results). With respect to the repetition of steps (i.e. number of samples analyzed or number of substrate regions), see *In re Harza*, (274 F.2d 669, 124 USPQ 378 (CCPA 1960)) where the court held that mere duplication of parts has no patentable significance unless a new and unexpected result is produced. With respect to the quantity of sample used, it is clear that the mere scaling up of a prior art process capable of being scaled up would not establish patentability in a claim to an old process so scaled *In re Rinehart*, 531 F.2d. 1048, 189 U.S.P.Q. 143 (C.C.P.A. 1976).

For ***claims 151 and 167***, Sharma et al. disclose the "optimization" of formulations (e.g., see Table I showing enhancement factor of 99000 for 50%DMβ; see also 60%HPβ, which has an enhancement factor of 10000 compared to only 2140 for 50% HPβ).

For ***claims 171 and 172***, Sharma et al. disclose at least three "solubilizing" excipients (e.g., see Sharma et al., page 1229, column 2, paragraph 1 wherein a mixed alkyl, hydroxyalkyl and carboxyalkyl ether derivatives are disclosed).

The prior art teachings of Sharma et al. differ from the claimed invention as follows:

For ***claim 136***, Sharma et al. fail to disclose **(a)(2)** samples at separate sites in the array or located at separate wells in the array. Sharma et al. also fail to disclose **(a)(3)** an array comprising at least 1,000 different samples. Furthermore, Sharma et al. fail to disclose **(a)(4)** preparation of an array via an automated system that adds and mixes the components of each sample under software control.

For ***claim 147 and 163***, Sharma et al. fail to disclose an array wherein each sample of the array has a total volume between 150 and 200 μl.

For ***claim 150 and 166***, Sharma et al. fail to disclose 1000 formulations per day.

For ***claims 152-154 and 168-170***, Sharma et al. fail to disclose data mining algorithms.

For ***claims 175-177***, Sharma et al. fail to disclose use of UV spectrometer.

However, the combined references of Merritt, Saneii et al., Wang et al., and Lipinski et al. teach the following limitations that are deficient in Sharma et al.:

For ***claim 136***, the combined references of Merritt, Saneii et al., Wang et al., and Lipinski et al. (see entire document) teach **(a)(2)** the use of separate wells on an array (e.g., see Merritt, page 1998, column 2, paragraph 1 wherein a microtiter plate is disclosed; see also figure 1). Furthermore, the combined references of Merritt, Saneii et al., Wang et al., and Lipinski et al. teach **(a)(3)** the use of over one million samples (e.g., see Merritt, page 1998, column 2, paragraph 1). In addition, the combined references of Merritt, Saneii et al., Wang et al., and Lipinski et al. teach **(a)(4)** the use of automated

system that adds and mixes the components of each sample under software control (e.g., see page 1998, column 1, last paragraph wherein Applicants' elected Tecan 5072 Robotic Sample Processor is disclosed; see also figure 1; see also page 507, "Who need a Computer" section). In addition, the Examiner notes "the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA1955). Also note that optimization of process steps, especially with respect to numbers of samples analyzed or numbers of substrate regions is within the routine skill of the art. *In re Burhans*, 154 F.2d 690, 69 USPQ330 (CCPA 1946) (selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results). With respect to the repetition of steps (i.e. number of samples analyzed or number of substrate regions), see *In re Harza*, (274 F.2d 669, 124 USPQ 378 (CCPA 1960)) where the court held that mere duplication of parts has no patentable significance unless a new and unexpected result is produced.

For ***claims 145-147 and 161-163***, the combined references of Merritt, Saneii et al., Wang et al., and Lipinski et al. disclose 100 ng of sample (e.g., see Lipinski et al., section 2.17, especially, page 15, column 2, last paragraph showing < 5μg/ml for 2.5 ml volume = ~ 12.5 μg; see also Merritt, figure 1). The combined references of Merritt, Saneii et al., Wang et al., and Lipinski et al. also disclose the use of a total volume between 150 and 200 μl (e.g., see Merritt, page 506, paragraph bridging columns 1 and 2; see also figure 1).

For ***claims 150 and 166***, the combined references of Merritt, Saneii et al., Wang et al., and Lipinski et al. disclose 1000 formulations per day (e.g, see Merritt, page 506, column 2, paragraph 1, "… over a period of two years the equipment was used to prepare about one million compounds for assay" i.e., 1,000,000/2 × 365 = 1369/day). In addition, the Examiner notes "the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA1955). Also note that optimization of process steps, especially with respect to numbers of samples analyzed or numbers of substrate regions is within the routine skill of the art. With respect to the repetition of steps (i.e. number of samples analyzed or number of substrate regions), see *In re Harza*, (274 F.2d 669, 124 USPQ 378 (CCPA 1960)) where the court held that mere duplication of parts has no patentable significance unless a new and unexpected result is produced.

For ***claims 152-154 and 168-170***, the combined references of Merritt, Saneii et al., Wang et al., and Lipinski et al. disclose the use of data mining algorithms (e.g., see Lipinski et al., section 2.3; see also section 3; see also section 4).

For ***claims 175-177***, the combined references of Merritt, Saneii et al., Wang et al., and Lipinski et al. disclose the use of UV spectrometer (e.g., see Lipinski et al., section 2.18).

It would have been prima facie obvious to one skilled in the art at the time the invention was made to use the commercially available robotic liquid handling devices disclosed by the combined references of Merritt, Saneii et al., Wang et al., and Lipinski et

al. to prepare and/or analyze the library of Pacltaxel/Cyclodextrin pharmaceutical drug formulations because the commercially available liquid handling devices disclosed by the combined references of Merritt, Saneii et al., Wang et al., and Lipinski et al. were explicitly designed for this purpose (e.g., see Merritt, column 1, paragraph 1, "The introduction of automation and increasing levels of miniaturization in the high-throughput screening (HTS) arena at the start of the 1990s provided the impetus for the development of combinatorial chemistry in drug discovery"; see also page 510, column 1, paragraph 1, "These techniques [automated HTS] have been embraced by medicinal chemists, and are now applied as part of the wide range of approaches available to tackle the discovery and development of new drugs), which would encompass the "development" of the Paclitaxel drugs disclosed by Sharma et al. Furthermore, one of ordinary skill in the art would have been motivated to use the commercially available liquid handling devices as disclosed by the combined references of Merritt, Saneii et al., Wang et al., and Lipinski et al. because according to the combined references these automated systems have numerous advantages for conveniently and reproducibly screening large numbers of samples with optimal controls by the practitioner to increase the speed and/or reduce the costs via, for example, the use of small sample volumes and fast computer automation (e.g., see Merritt, page 507, column 2, last paragraph, "... instead of developing a single piece of equipment to perform all the functions of the synthetic process we had separated the functions into stand-alone modules. This allowed more-flexible equipment scheduling and use"; see also Wang et al., paragraph bridging pages 1125 and 1126, "Our ease of acquiring FIA-MS data on samples 8 in a time of less

than one minute suggested the possibility of processing an entire microtiter plate in less than 10 minutes (providing at least a four-to-five-fold speed advantage over existing technologies). However, to maintain this speed advantage, it was critical to develop tools to facilitate automated data acquisition and data processing … To permit autosampling of eight samples at a time, an Excel ™ macro was used to automatically convert a text file, containing information about the expected products in each well of a microtiter plate, into a format amenable to automated data acquisition and data processing of eight samples at a time"). In addition, this automation is particularly important for solubility studies (e.g., see Lipinski et al., section 5, especially page 23, column 2, especially first full paragraph, "… we believe a competitive advantage accrues to the organization that can identify compound sets likely to give leads more easily converted to orally active drugs [i.e., water soluble]"; see also section 2.15, "High throughput screening hits, calculations and solubility measurements"; see also abstract), which would encompass the solubility studies disclosed by Sharma et al. Finally, one of ordinary skill in the art would reasonably have expected to be successful because the combined references of Merritt, Saneii et al., Wang et al., and Lipinski et al. disclose that automated robotic liquid sample handling devices are compatible with, and routinely used in, a wide variety of chemical applications and are especially useful in the pharmaceutical industry (e.g., see Merritt, page 510, column 1, last paragraph, "These techniques have been embraced by medicinal chemists, and are now applied as part of the wide range of approaches available e to tackle the discovery and development of new drugs"; see also Saneii et al., last two paragraphs, "From the foregoing it will be seen that the apparatus of the present invention

is highly flexible and is capable of synthesizing a variety of compounds in a single setup or producing a larger quantity of a single compound in the wells").

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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October 30, 2005

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